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VALENTINE MOTT

UNIV OF MICH.

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VALENTINE MOTT

Prior to the introduction of anæsthesia (1847), modern English and American surgery was mainly occupied with ligations of arteries and excisions of bones and joints. On the Continent, other things were done, particularly in subcutaneous and plastic surgery; but in our own country, the story of these earlier days is centered in the bold performance of difficult, dangerous operations by rugged pioneers, whose powerful arms were as much employed in holding down the writhing, screaming patient as in plying the needle and the scalpel. Our history begins in 1796, when Dr. Wright Post, of New York, for the first time in our country, ligated the femoral artery for aneurism by the Hunterian method, to be followed by his equally successful ligations of the primitive carotid (1813, 1816), the external iliac (1814) and the subclavian (1817). In 1781, Dr. John Warren, of Boston, amputated at the shoulder joint. A few years later, in the backwoods of Kentucky, Dr. Ephraim McDowell performed his first ovariotomy (1809) and Dr. Charles McCreary first excised the clavicle with success (1813). What followed thereafter is a long and complex history of brilliant operating, culminating in the foundation of operative gynecology by a country doctor in South Carolina, Marion Sims. Of this group of pioneer surgeons, the most remarkable was unquestionably Dr. Valentine Mott, whose skill in operating was derived from two great teachers, Wright Post and Astley Cooper. Mott performed no less than 138 ligations of the great vessels for aneurism, 165 lithotomies and over 1,000 amputations. What is more to the purpose, his

patients usually recovered and lived. In 1818, to save the life of a sailor then under operation for subclavian aneurism, Mott ligated the innominate artery, two inches from the heart, with survival of his patient for 28 days. Thereafter, he tied the femoral 57 times, the primitive carotid 51 times, the popliteal 10 times, the subclavian 8 times, the external iliac 6 times, the carotid and internal iliac twice each, and the common iliac once. On June 17, 1828, he excised the clavicle for osteosarcoma with tough adhesions, a bloody four-hour operation, requiring 40 ligations of arteries, yet with complete recovery of his patient. In 1821 he performed the first operation for osteosarcoma of the lower jaw, was the first to excise it for necrosis, and in 1832, introduced his operation for immobilizing it. He successfully amputated at the hip-joint in 1824 and removed a large fibroid tumor from the nasopharynx in 1841. This is a brilliant record indeed, particularly in getting surgical patients well, without anæsthesia or antisepsis. It placed Mott on a level with the greatest European surgeons of his time, who received him with a respect and consideration rarely accorded Americans in those days. Mott's teacher, Sir Astley Cooper, said: "He has performed more of the great operations than any man living, or that ever did live."

Valentine Mott, son of Dr. Henry Mott, a physician of English descent, was born at Glen Cove, near Oyster Bay, Long Island, on August 20, 1785. He got his schooling by private tuition at Newton, Long Island, and was a good Greek and Latin scholar all his life. In 1804, he began to study medicine under Dr. Valentine Seaman, of New York, and in 1807 took his M.D. at Columbia College with a graduating dissertation on the therapeutic properties of the marsh rosemary (*Statice limonium*). After the usual years of study at London and Edinburgh, where he came under Astley Cooper, Monro, Home, Hope and Dugald Stewart, he became, at the age of 26, professor of surgery in Columbia College (1811), occupying the chair until 1826, when the whole faculty resigned to form the Rutgers Medical College, of New Jersey. In 1831, when the Rutgers College closed, Mott was appointed professor of operative surgery in the College of

Physicians and Surgeons. The hazards of the kind of bold surgery he was then doing broke down his health in 1834 and he spent the next six years in travel through Europe and Asia. He was a good traveler, putting up with hardship with cheerfulness and equanimity, and probably saw more of real conditions in Greece, Asia Minor and Egypt than any other American of his time. After considerable exposure to bubonic plague in the near East, and having made fast friendships with all his surgical peers, he returned in 1841, to accept the chair of surgery in Medical College of the University of New York, which he held until 1850, when he went abroad again. Upon his return, he became professor of operative surgery in the College of Physicians and Surgeons, continuing later, as emeritus professor in this chair, until his death on April 26, 1865. Two of his sons, Valentine and Alexander Brown Mott, were physicians, of whom the former served as a surgeon in the Sicilian rebellion and died of yellow fever in California in 1854. The latter was one of the founders of Bellevue Medical College. Dr. Mott's widow converted his libray and museum of pathological specimens into a memorial at 64 Madison Avenue in 1866. The collection was transferred to the Academy of Medicine in 1909.

Dr. Mott was a fine figure of a man, with an open winning countenance in youth, an urbane, attractive gentleman whose later portraits resemble those of well-born Englishmen of the period. He was a good, careful teacher, popular with the students, whom he advised never to attempt a dangerous operation without first considering whether they would care to undergo it themselves. In his travels, he notes with aversion the tendency of continental surgeons toward showy operating with a callous disregard for the patient's recovery. He was not that kind of a man. We should not recount his surgical triumphs to-day, were it not for his wonderful record of recoveries due to constant solicitude for his patients. His wit in the surgical clinic was of the period. On one occasion, when he was consulting with the mother of a dirty, emaciated child, a half-bred student jumped the rail of the amphitheatre and began to examine the naked infant himself. Wheeling about suddenly, Mott said: "Are *you*

the father of this child?" Amid the derision of his fellows, the blushing student made an ignominious retreat to the back benches.

Gross, in his eulogy of Mott, notes only one fault: "As a lecturer, he is said to have occasionally been too egotistical." And thereby hangs a tale. The pioneer period before the Civil War was one in which the possibilities of developing the boundless resources of our country filled every mind, an uncritical, sanguine, spread-eagle period to which Arthur Hugh Clough reacted with the express conviction: "Emerson is the only profound man in this country." Emerson himself said, in his lectures: "The American eagle is well, but beware of the American peacock." In his letters to Carlyle, he says that the trouble with Americans of the period is "not water on the brain, but a little gas there." Yankee Doodle, our then popular national air, affected the Austrian poet Lenau as "a stiff bear dance," in other words, a good quickstep for troops hiking to war, but droll for state occasions. To Henry James, the sculptures and paintings in the rotunda of the Capitol were "touching reminders of the early period of American art." Upon this queer period of wind-bag oratory, Mott fell with a single obsession: priority in surgical procedure. His was nowise an unfinished mind, but this subject affected him as with the anatomist Pieter Camper, who, in investigating the osteology of whales, began to see even pretty girls as modifed whales. Mott's case-reports are clear, precise, unaffected and simple, but his travels are full of ludicrous self-adulation about his operations, to which he constantly recurs. Yet he was timorous about writing a surgical text book. He was wise. His best work is recorded in his additions to his huge translation of Velpeau's Surgery (1847), which is now our great source-book for the history of surgical operations.

We read that Mott's Travels in Europe (1842) exposed him to "severe and ungenerous criticism from the medical press." I have waded through this stodgy volume of 425 pages, and my reaction to it is that of Falstaff: an intolerable deal of verbiage to a half-pennyworth of facts. The positive facts I glean from the tedious perusal are that dolphins were sacrificed to Ceres at

Phalerus, that a true Greek girl never dances except with her own sex, that modern Greeks sing with a nasal twang, that medical students in Rome went about the clinics with jars of live coals to keep them warm, that Egyptians, like the Spaniards, keep their houses cool by shutting out the hot air and light, that fat men are rare in Egypt, that Mohammed Ali had women trained in midwifery for exclusive harem practice, and that a Turk made lime out of the marble pavement of the Theseion in 1769. Jesting apart, for a "big, strong, healthy man," Mott writes in this book in what Lady Dufferin called the Honorable Impulsia Gushington manner, the Laura Matilda vein affected by young ladies of the keepsake period, who half-memorized Burke's Peerage and Roger's "Italy." The volume is padded throughout with that gratuitous parade of classical lore which disfigured even the prose of Poe. The longest chapter, that on Greece, is stuffed with guide-book information, trite mythology and triter citations from Childe Harold. When Mott tells how the unscrupulous Dupuytren got hold of his paper on excision of the jaw and then tried to shoulder him out of his priority, he does it with the fussy italics of maiden ladies in Victorian novels. The sound and readable parts of the book are his fine and generous pictures of his great surgical colleagues abroad, his accounts of goitre, pellagra, the marsh-fevers of Greece and Italy, his reasons for interdicting the Italian climate for consumptives, his view that, in antiquity, leprosy and lues were probably identical, his generous speculations on the futility of quarantine in malarial fever and of disinfection against bubonic plague. His vision was keen enough, his literary style eminently genteel, but it takes him a page to tell us that Hell-Gate is a fiercer current than that between Scilla and Charybdis, the centric fact being buried in a cocoon of verbiage. He is humorous only about the smell of vagrant Greeks, the large-sized bed-bugs on the plains of Marathon and the obesity of women in Asia Minor. He damns the ambitious Venetians and Lord Elgin for despoiling the Parthenon in most elegant language and his references to nudity are invariably stilted. Of the Venus dé'Medici, he complains that "it is too diminutive, while Canova's Venus is better be-

cause there is more of it." Pauline Borghese (Napoleon's sister), who posed for the statue, would have smiled at this tribute. The Theseion at Athens is too small for him and only the Pyramids come up to his expectations. In Florence, however, he notices a misplaced inguinal artery in a wax preparation, and goes straight to the correct inference, *viz.*, that since the time when the great Quattrocento painters practised dissection, anatomical teaching at Florence seems to have been concentrated mainly on the muscles. The most interesting thing in Mott's book is his account of the petrified pathological preparations of the Florentine Sigato. This Signor Sigato, it seems, had acquired in the far East a secret process of petrifying animal substances, so that pathological preparations, thus hardened, could be sawed into slabs, susceptible of a high polish, preserving at the same time the most delicate details of structure and color, even to the bloodvessels. Mott describes a table-top, a mosaic of squares, showing perfect cross-sections of a phthisical lung, hydatids of the liver, renal calculus and cardiac lesions. The petrified solid specimens could be thrown about in the roughest way without damage. Mott tried to employ Sigato, who was heavily in debt, but the unfortunate Florentine died three weeks later and his wonderful secret died with him. If it could be rediscovered, what wonderful archives in polished stone would be conveyed to posterity by pathologists and cross-section anatomists!

F. H. Garrison

THE APPLICATION OF NEWER METHODS IN BLOOD-CHEMISTRY TO CLINICAL MEDICINE

Renee von E.-Wiener

(Delivered before the New York Academy of Medicine, May 21st, 1925.)

The blood together with the lymph provides a vehicle for the chemical correlation of the cells of the body. Any changed condition in the tissue fluids will be promptly reflected in its composition and conversely any change in the basic constituents of

the blood will affect the composition of the tissue fluid and hence of the tissue juice within the cells. Disturbances in the function of the organs of elimination as well as abnormalities in the intermediary metabolism of the body will affect the composition of the blood.

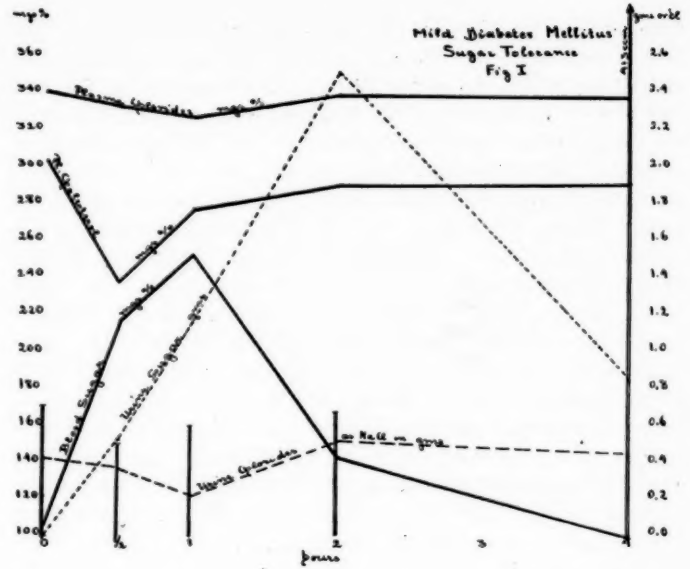
The composition of the blood is also materially affected by the ingestion of food and the intensity of the catabolic processes. While the concentration of certain basic components such as water, inorganic salts and proteins is affected to only a slight extent, the concentration of food substances being conveyed to the tissues as well as the concentration of waste material varies within wider limits and for a greater period of time. It follows that for very exact work a diet of standard chemical composition for a few days preceding the blood test is necessary, for clinical work it suffices to obtain the sample from the subject in a morning fasting condition. For a determination of the basic constituents which are only transitorily affected by food ingestion a three hour interval between food intake and securing of blood sample is sufficient. About 80 per cent. of the blood is water. Various gases, inorganic salts and organic compounds are held in true solution. The more complex organic compounds, such as proteins, higher carbohydrates, lipoids, etc., are held in colloidal solution, while fats, especially shortly after absorption, are present in finely emulsified form. Structurally the blood is a suspension of cellular elements in this heterogenous solution, the plasma. The components of the blood, most of which are present in minute concentrations, are unequally distributed between the corpuscles and the plasm. Certain organic as well as inorganic components do not penetrate the erythrocytes or if so only in extremely small proportion. Fatty acids and lipoids as well as the plasma proteins are also adsorbed to a certain extent on the surface of the erythrocytes. It is best to employ plasma rather than whole blood for the quantitative determination of its constituents, except for those components which are present in nearly equal or even greater concentration in the corpuscles than in the plasma. Many of the blood constituents of clinical importance are present in minute concentrations and the need of pre-

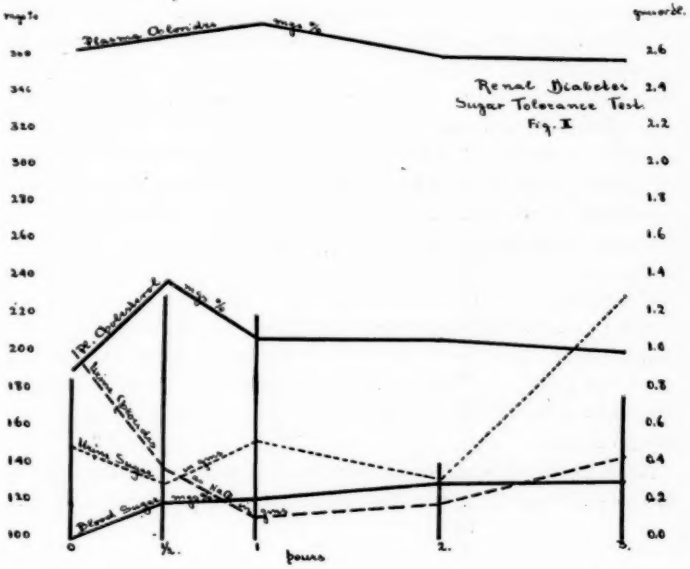
cautionary measures to avoid contamination by foreign substances must be realized. When the blood is obtained from the subject not in a morning fasting condition but after a three hour fast the time when the last meal had been completed and the amount of food taken expressed in gms of carbohydrate, protein and fat should be noted. To insure that the Luer syringe as well as the needle employed are chemically clean and sterile, the syringe must be washed with tap water, followed by two rinsings with distilled water and dried over night at a temperature of 110° Cent. The needles may be dried with alcohol and ether. Sterilization by boiling in tap water does not insure a chemically clean apparatus and causes errors not only in the calcium determination but also in other analyses of the blood. Before delivering the drawn blood into a chemically clean and sterile glass flask, containing a measured amount of anticoagulent, the needle should be detached to avoid damage to the blood corpuscles.

The use of Sodium citrate as anticoagulent does not interfere with the determination of plasma Calcium, nor does it render the determination of plasma Fibrinogen more difficult, as is the case when oxalate is used. The employment of Sodium citrate as anticoagulent is entirely satisfactory only if it has been recrystallized, finely ground in a steel or agate mortar, and introduced into the flask in a dry state. Introduction of the citrate in solution and allowing it to dry causes the formation of larger crystals which dissolve too slowly when the blood is added. The minimum amount of Sodium citrate which will prevent coagulation is 4 mgs per ccm of blood, the maximum amount which may be used without danger of causing hemolysis or affecting certain determinations is 10 mgs per ccm of blood. For clinical work it is best to keep within the limits of 4 to 8 mgs per ccm of blood. For research work a constant proportion must be maintained.

While determinations of a single component are often of clinical value in following a case, a more complete picture is obtained by a coincident analysis for the concentration of other elements, and the diagnostic value of the quantitative anaiysis may thereby be enhanced.

Such analyses have been made for a number of years and the determinations shown in the following tables were chosen as rep-


Mild Diabetes Mellitus
Sugar Tolerance
Fig I
Plasma Chlorides mgs %
Blood Sugar mgs %
Urine Sugar gms
Urine Chlorides gms
Urine Volume cc
hours


Plasma Chlorides mgs %
Renal Diabetes
Sugar Tolerance Test
Fig. II
Blood Sugar mgs %
Urine Sugar gms
Urine Chlorides gms
Urine Volume cc
hours

resentative from a great number of cases. Table I gives the determinations of the Blood Sugar, Plasma Calcium, Chlorides and Cholesterol and the Serum Proteins in Glucosuria, *i.e.*, uncomplicated Diabetes Mellitus, Diabetes Mellitus with complications and the so-called Renal Diabetes. On the first line of the table the limits of normal concentrations are shown. It is interesting to observe that while the Plasma Calcium in uncomplicated Diabetes Mellitus is at the high normal level, if not actually increased, in the cases complicated by Arterio sclerosis and Myocardial insufficiency it is almost always at the low normal level or decreased below the normal concentration. In renal diabetes the Calcium concentration remains within the normal limits. The chlorides in true Diabetes Mellitus are usually decreased below the normal level while in the renal diabetic cases they are increased above the normal limit or at least a high normal. One case of renal diabetes was put on a salt free diet. The chloride concentration became normal and the calcium, which had always been within the normal limits increased slightly above the normal. The concentration of the sugar in the urine decreased from an average of 2 per cent. with a blood sugar of 100 mgs per cent. to an average of 0.8 per cent. with the same blood sugar concentration. The volume output remained the same and the decrease in percentage cannot be ascribed to greater dilution. The concentrations of the Serum Proteins are high in Diabetes Mellitus and in Renal diabetes, especially the Albumen fraction. Coincident with the decrease in the Calcium concentration in the complications mentioned the Albumen fraction is also found decreased. The Cholesterol in true diabetes is usually increased in Renal Diabetes it is normal.

The changes in the concentrations of Blood Sugar, Chlorides and Cholesterol as well as the excretion of Sugar and Chlorides in the Urine have been followed during Sugar Tolerance tests on true diabetics and renal diabetics. Figure I shows the typical curves of mild diabetes mellitus, figure II those of renal diabetes. The curves have been selected as characteristic from a total of twenty cases.

Aside from the characteristic and well known difference in the blood sugar curve, there is also a difference in the cholesterol and

in the chloride curve. In cases of diabetes mellitus there is usually a slight drop in the chlorides and a drop in the cholesterol 30 minutes after glucose ingestion. The true renal diabetic at 30 minutes post glucose ingestion shows a decided rise in cholesterol and a slight rise in the plasma chlorides, resembling the normal but in a more accentuated form. The curves of sugar excretion of these types also varies. In true diabetes mellitus the curve reaches its peak shortly after the blood sugar curve has passed its peak and at the fourth hour the excretion is materially decreased. In renal diabetes the peak of the sugar excretion is not likely to be reached or passed within the period of the experiment. The chloride excretion curves do not differ materially. The volume output also differs. It is delayed in diabetes mellitus while in renal diabetes the fluid taken is excreted to a great extent in the early period of the experiment. The vertical lines in Figs. I and II indicate the volume output. There was no change observable in the concentration of Calcium or Serum proteins other than that accounted for by a very slight change in cell volume. This observed change of fluid to cell mass in the blood was however not sufficiently great to account for the changes in the chloride and cholesterol concentration.

The cases of impaired kidney function (Table II) may be divided into two main groups: the azotaemic type and the hydraemic type.

In the azotaemic type the serum proteins are a low normal or slightly decreased. There is no consistent decrease in the calcium concentration nor increase in the chloride concentration. The fibrinogen is slightly increased. Subjective symptoms and clinical examination frequently lead to the presumption of the existence of a focus of infection in the absence of focal symptoms. In such cases the determination of cholesterol and fibrinogen as well as the sedimentation rate is of considerable clinical value especially if interval analyses are made. With azotaemia there is always a reduction in the concentration of the urine uric acid excretion which may be compensated for by an increase in the volume output, without a marked or consistent uricacidemia.

The simultaneous determination of uric acid in the blood and urine as well as the determination of the urine uric acid excreted

during twenty-four hours is of value not only in cases of renal insufficiency but also in uricacidemia without retention of other nitrogenous metabolites. The kidneys in health concentrate uric acid approximately twenty times but concentration as high as sixty times may occur. An excess supply of uric acid of endogenous or exogenous origin may raise the blood uric acid concentration even in the absence of renal insufficiency. Again, with a limited supply of uric acid and an increased volume output its content in the blood may not be raised beyond the high normal level despite a decreased ability of the kidneys to concentrate it. The two factors, production of uric acid in the tissues and possible destruction in the blood or special organs, on the one hand, and excretion by the kidneys, on the other hand, are quite unrelated.

If the blood and urine specimen are obtained from the subject, one hour after the first voiding and in a morning fasting condition, which includes fasting from water, the ratio "mgs per cent. Urine Uric Acid / mgs per cent. Blood Uric Acid" will normally lie between 20 to 35. The ratio "mgs Uric Acid in 24 hrs. / mgs per cent. Blood Uric Acid" on a purine free diet for a healthy individual is 250 to 350. In mild kidney deficiency the single specimen ratio will always be low, while the twenty-four hour ratio, due to an increased volume output may be normal, and the blood uric acid not increased above the high normal level.

The hydraemic type may again be divided into two groups. "A" The chloride content of the blood is materially increased while the serum proteins are not reduced or only very slightly so. "B" The chloride concentration is normal or only slightly increased but the concentration of the Se. proteins, especially the albumen fraction, is very much lowered. The calcium concentration is below normal and the fibrinogen and cholesterol are very much increased. Determinations on this type are shown in table II. In this group of cases there is decided retention of water in the tissues and this is due to a defective osmotic-filter apparatus, that is reduction of serum protein concentration, which may be followed or accompanied by a slight chloride retention. The nitrogenous waste products are not increased, or

only slightly so, the alkali reserve, the pH and the inorganic phosphorus are normal or only very slightly changed. The usual tests for renal function, except water and NaCl elimination, are normal or only slightly subnormal. The cell volume of the blood is usually not reduced. The reduction in the Se. proteins occurs to the largest extent in the albumen fraction and the ratio "Albumen/Globulin" is therefore materially decreased. A ratio below 1 is often encountered; a ratio below 0.5 indicates a severe condition. The fractionational precipitation of the proteins must be carried out immediately after the sample has been obtained. If the blood or plasma is allowed to stand, especially if exposed to sunlight or if an excess of anticoagulent has been used, a change in the solubility of the albumen fraction may occur which causes a reduction in its concentration and an increase in the concentration of the globulin fraction.

The decrease in the calcium conc. runs parallel to the decrease in the albumen conc. The rise in the fibrinogen and cholesterol recalls the increase in these substances observed in chronic infections. Coincidently the sedimentation rate is very much increased. Improvement in the condition is reflected by a decrease in the sedimentation rate and repeated estimations of the rate in such cases, as in cases of infectious diseases, *e.g.*, T. B., furnishes a guide, other things being equal, of the progress or retrogression of the disease.

Blood chemistry determinations in the toxemias of pregnancy are shown in table III. The average typical concentrations which obtain during the course of a normal pregnancy are shown as well as blood chemistry estimations representative of the four types of Toxemias.

In normal pregnancy there is a steady increase in the cholesterol and fibrinogen conc. progressively during the pregnant term. There is a reduction in the cell vol. and this reduction may account for the slight decrease in plasm Ca. concentration towards the termination of the pregnancy. The chloride concentration in normal pregnancy is increased above the normal during the later months. There is a slight reduction in the Se. proteins but the ratio Alb./Glob. remains normal.

The Toxemias may be divided into four groups: "A" Vomiting of pregnancy, "B" Toxemia with retention, "C" Toxemia with uricacidemia, "D" Eclampsia.

"A." Depending upon the severity of the vomiting the chloride content of the blood may be increased if the loss of fluid is relatively greater than the loss of HCl from the stomach, or decreased if the reverse is the case, a secondary factor being the degree of chloride storage in the tissues. Slight acidosis is often present. The normal increase in cholesterol in pregnancy is absent and in the severer cases the cholesterol is decreased below the concentration normal for non-pregnant women. Long continued vomiting (pernicious) may result in an accumulation of nitrogenous waste products in the blood.

"B." In this group there is definite retention of non-protein nitrogen, urea, uric acid and occasionally creatinine. The fibrinogen shows the usual increase during pregnancy, it may be slightly accentuated. The increase in cholesterol is normal. The uric acid ratio is of the retention type. That is to say, the blood uric acid may be increased or merely high normal with a lowering of the per cent. excretion of the uric acid in the urine.

"C." This type of cases have definite uricacidemia but no other nitrogen retention. The fibrinogen is increased above the rise in concentration usually present during pregnancy. The cholesterol may be far above the normal pregnancy cholesterol level. The icterus index may be increased above the index normal to pregnancy and the Van der Bergh test for bile acids may show the presence of bilirubin in a concentration greater than 0.5 mgs per cent. The urine uric acid to blood uric acid ratios show that the kidney potential for concentration of uric acid is either not at all or only slightly impaired and that the high blood uric acid is not due to a decrease in the excretion of uric acid by the kidneys below the normal concentration.

"D." In eclampsia there may be a moderate azotaemia but the uric acid is the only nitrogenous metabolite that is ever excessively increased. The calcium concentration is decreased, the chloride concentration is usually low but sometimes normal. The cholesterol may be increased or be normal for the period of

gestation. If the concentration of the calcium and the chlorides are expressed in millimols the product of the calcium concentration and the square of the chloride concentration is a constant within narrow limits in health as well as in many pathological conditions. This constant is reduced in acidosis, diabetic coma, uremia and eclampsia; in fact in all conditions involving a change in the reaction of the blood. The degree to which this constant varies from the normal seems to indicate the degree of acidosis present.

The determination of fibrinogen and of cholesterol as well as the sedimentation rate is of value in cases of proven or of suspected infection in which there are no definite or general focal symptoms. In acute infections the fibrinogen is high and the cholesterol at first is low. The defensive mechanism of the body seems to involve a rise in the cholesterol concentration and in chronic infections which are being actively combatted by the body the cholesterol is always increased above the normal. In certain infections, *e.g.,* tuberculosis, the calcium concentration is decreased below the normal. In furunculosis there is usually a definite decrease in the cholesterol concentration.

In diseases of the skin the estimation of the uric acid, sugar, calcium and cholesterol may be of clinical assistance. In urticaria, angio-neurotic edema and dermatitis the calcium is usually decreased below the normal, in acne its concentration remains at the high normal level.

In gout the blood uric acid is more or less increased, but its deviation from the normal level is not as marked as is the decrease in the urinary concentration of uric acid, especially just preceding an acute attack. The fibrinogen is considerably increased. The calcium is usually slightly decreased but increases above the normal just preceding an acute attack have been found.

The sedimentation rate is increased in many pathological conditions, and by itself is therefor not of much diagnostic value. The fibrinogen is not the only substance which by its increased concentration causes an accelerated rate. The globulin frac-

tion, cell volume, viscosity and the pH as well as a certain unknown factor which causes a decrease in the sedimentation rate also play a part in determining the rate at which agglutination and sedimentation take place. Many instances of "reduced sedimentation rates" with normal cell volumes, normal protein concentrations and even increased fibrinogen have been encountered. In most of these cases indicanuria was present and the feces examination in some was said to show a high histamine content. It is possible that the unknown factor which decreases the rate of sedimentation may prove to be the presence of an increased amount of an anti-agglutinating substance in the blood. Such chemical bodies are found among the products of protein putrefaction and at least one, histamine, is known to lower the coagulability of the blood.

The cell volume estimation is a valuable aid in the proper interpretation of the blood chemistry figures; in fact in certain cases determination of the water content may also prove advisable. In the methods that are commonly used for the estimation of substances in the protein free filtrate the volume occupied by the precipitate is not taken into account and the filtrate is considered as though occupying the volume of the original precipitation mixture. This introduces an error which may be disregarded as long as the variations in cell volume remain within the normal limits, since the values are comparable. If the cell volume and hence the precipitate are much reduced the error inherent to this method is also reduced and conversely if the cell volume is increased the error is increased. Ten ccm. of the filtrate obtained by the Folin and Wu precipitation method from a blood with a cell volume of 50 per cent. will contain the soluble substances present in about 1.67 ccm. of blood and not 1 ccm. as is assumed in the calculation. Conversely if the cell volume is much reduced, let us say to 22 per cent., ten ccm. of such a filtrate will contain the soluble substances present in approximately 1.25 ccm. of blood. The smaller the so-called dry volume, *i.e.*, the precipitate, the closer the approach to the theoretical value. Adsorption of the soluble substances on the protein pre-

cipitate is indeterminate but in any case could never compensate for the above mentioned source of error. The variations in the cell volume usually encountered are not sufficiently large to affect the comparative values; but the influence of a reduced cell volume and hydraemia on the final results of the analyses should be taken into account. Thus the often mentioned low urea and sugar concentration in pregnancy may be attributed in part at least to this effect.

The determination of viscosity and surface tension are physico-chemical measurements which may prove of value.

Ionic antagonism is a phenomenon of great importance in life processes and the determination of the other cations present, aside of calcium, should be undertaken. The concentration of resorbed intestinal toxins as well as the enzymatic activities taking place in the blood stream, are subjects which also may prove worthy of future investigation.

Supplemented by Urine chemistry, by the chemistry of the Respiration and by Metabolic Rate estimation, blood chemistry offers the best means of investigating the status of the chemical equilibrium of a living organism and chemically correct and critically interpreted blood analyses will be found to have a wide and valuable clinical application.

TABLE I

BLOOD CHEMISTRY IN GLUCOSURIA

	Bl. Sugar mgs. %	Cell vol. %	Plasma Ca. mgs. %	Cl. mgs. %	Chol. mgs. %	Fib. mgs. %	Serum Alb. %	Glob. %	Tot. Protein %	Ratio Alb./Gl.	Urine Sugar at time of blood	
Low Normal	80	42.0	9.8	355	150	250	4.8	1.8	6.6	2.8	.....	
High Normal	100	48.0	10.3	365	165	325	5.5	2.6	8.1	1.8	.....	
Diabetes Mellitus												
No. 2608	384	55.3	10.4	350	250	400	5.30	2.98	8.28	1.8	xxxx	
No. 2361	125	37.5	10.6	343	240	.....	5.64	1.58	7.22	3.5	0	
No. 2144	333	43.6	10.1	331	220	340	4.71	1.83	6.54	2.6	0.8%	
" "	138	46.0	10.4	335	210	.....	4.78	1.73	6.51	2.8	0	
No. 1675	268	35.0	10.2	344	.....	455	4.69	2.37	7.06	2.0	xxxx	
" "	200	35.1	10.1	327	344	.....	4.56	2.12	6.68	2.1	0	
" "	510	36.1	9.6	318	345	383	4.08	2.75	6.83	1.5	4.0%	CO_2 25.5 vol. %
No. 2291	182	37.7	9.7	350	228	455	5.22	2.45	7.67	2.1	tr.	Art. scler.
No. 2529	196	35.0	8.8	318	269	278	3.40	1.83	5.23	1.9	x	Myocard. Art. scl.
No. 2006	174	31.8	9.4	350	.....	.....	.....	.....	.....	.....	tr.	Myocard. Art. scl.
No. 2348	210	40.0	9.5	346	232	555	3.80	1.40	5.20	2.7	x	Myocard. Ins. T. B.
No. 2534	222	39.5	11.1	340	166	590	4.70	2.37	7.07	2.0	xxx	Gangrene
No. 2566	174	45.0	10.6	350	.....	.....	4.15	1.40	5.55	2.9	0	Albuminuria
Marg.	149	45.3	10.7	360	180	288	4.35	2.60	6.95	1.7	0	Retinal Hem.
Renal												
No. 2595	80	48.5	10.3	361	156	278	5.93	1.58	7.51	3.8	0.95%	
No. 2312	103	43.2	10.3	365	228	346	5.50	1.94	7.44	2.8	2.00%	
" "	108	41.5	11.5	350	160	.....	6.00	2.04	8.04	2.9	0.80%	SALT FREE DIET
" "	100	40.7	10.0	383	.....	.....	5.50	1.84	7.34	3.0	2.00%	DIET DISCONTINUED
No. 2584	133	46.5	10.7	372	155	.....	5.80	1.60	7.40	3.6	0.70%	
No. 2269	87	42.5	9.8	360	150	245	5.00	2.18	7.18	2.3	x	

TABLE II

BLOOD CHEMISTRY IN IMPAIRED KIDNEY FUNCTION

	Cell vol. %	N.P.N. mgs.%	Blood Uric Acid mgs.%	Creat. mgs.%	Plasma Ca. mgs.%	Plasma Cl. mgs.%	Plasma Chol. mgs.%	Plasma Fibr. mgs.%	Serum Alb. %	Serum Glob. %	Serum Total Prot. %	Serum Ratio Alb./Glob.	
Low Normal	42.0	25.0	1.5	1.3	9.8	355	150	250	4.80	1.80	6.60	2.8	
High Normal	48.0	35.0	2.5	1.7	10.3	365	165	325	5.50	2.60	8.10	1.8	
Azotemic													
No. 06176	31.5	43.7	2.8	.....	8.7	367	.....	578	2.78	1.92	4.70	1.5	Albuminuria
Dol.	41.0	45.2	4.6	1.8	9.7	365	200	238	.....	.....	.....	.....	
No. 7298	34.7	47.0	3.6	3.0	9.0	373	357	532	3.07	2.49	5.56	1.2	
Stan.	36.0	53.0	4.8	2.4	10.2	365	175	465	4.20	2.20	6.40	1.9	
Orl.	30.0	80.0	5.0	5.4	.....	.....	.....	530	3.17	3.03	6.20	1.0	
No. 2563	21.0	123.0	5.7	4.3	10.2	386	225	447	4.08	2.45	6.53	1.6	
No. 73816	27.0	158.0	5.4	4.9	11.1	361	139	500	5.08	3.52	8.60	1.4	
Hydraemic													
No. 2616	42.0	35.5	1.5	.....	8.1	413	417	520	1.87	2.04	3.91	0.9	
Fol.	25.8	.....	.....	.....	8.3	360	251	655	1.58	4.37	5.92	0.4	
No. 2420	26.7	.....	.....	2.0	10.0	.....	150	853	3.36	4.20	7.56	0.8	
No. 2465	33.0	34.8	2.5	.....	8.7	360	425	1000	1.46	1.34	2.80	1.1	
" "	44.0	.....	.....	.....	9.2	.....	400	770	2.34	1.33	3.56	1.8	
" "	44.0	38.0	3.6	.....	8.9	381	491	590	2.07	1.05	3.12	2.0	
" "	40.1	41.5	2.0	.....	7.6	380	278	650	2.18	2.12	4.30	1.0	

TABLE III

BLOOD CHEMISTRY IN PREGNANCY

	Cell vol. %	BLOOD N.P.N. mgs.%	Uric Acid	Creat. mgs.%	Sug. mgs.%	PLASMA Ca. mgs.%	Cl. mgs.%	Chol. mgs.%	Fibr. mgs.%	SERUM Alb. %	Glob. %	Total Prot. %	Ratio Alb./Glob.	
Normal Pregnancy														
3½ ms.	33.3	.....	.....	.....	.....	10.2	358	168	334	5.33	1.84	7.17	2.9	
4 ms.	35.4	.....	.....	.....	.....	10.2	368	278	407	5.04	1.52	6.56	3.3	178
5 ms.	36.0	.....	.....	.....	.....	10.3	377	168	665	4.58	1.81	6.39	2.5	465
6 ms.	36.0	.....	.....	.....	.....	10.2	365	232	339	4.87	2.27	7.14	2.2	
7 ms.	32.0	.....	.....	.....	.....	10.2	380	214	455	4.64	1.93	6.57	2.4	439
8 ms.	34.0	.....	.....	.....	.....	9.8	374	266	555	4.90	2.25	7.15	2.2	
term	30.0	.....	.....	.....	.....	9.9	366	290	560	4.31	1.84	6.15	2.3	
Vomiting														
Mu. 4 ms.	38.0	27.0	1.2	.....	.....	11.1	350	120	350	.....	.....	.....	.....	
McG. 5 ms.	29.0	40.0	5.9	.....	.....	9.4	343	133	428	.....	.....	.....	.....	Pl. CO_2 40.0%
Ka. 5 ms.	15.4	22.2	4.1	.....	80	8.2	382	91	312	4.01	1.75	5.76	2.3	Pl. CO_2 40.0%
" 6 ms.	21.3	27.2	4.0	.....	.....	8.4	383	104	416	4.04	2.04	6.08	2.0	Pl. CO_2 45.0%
Azotemic														
Bla. 3 ms.	22.0	94.0	3.8	3.9	91	10.5	394	200	453	4.76	2.29	7.05	2.1	
Con. 5 ms.	33.0	44.5	7.2	.....	.....	8.8	360	.....	612	4.32	1.67	5.99	2.5	
" 6 ms.	37.7	55.0	7.3	.....	.....	9.4	.....	317	553	3.80	1.77	5.57	2.1	
" 7 ms.	29.6	40.0	8.3	1.5	.....	8.6	.....	268	454	3.56	1.77	5.33	2.0	
K. J. 9 ms.	30.0	53.5	5.9	1.4	.....	8.8	335	198	702	2.75	2.90	5.65	0.9	

TABLE III—(*Continued*)

	Cell vol. %	Blood N.P.N. mgs.%	Uric Acid mgs.%	Creat. mgs.%	Sug. mgs.%	Plasma Ca. mgs.%	Cl. mgs.%	Chol. mgs.%	Fibr. mgs.%	Serum Alb. %	Glob. %	Total Prot. %	Ratio Alb./Glob.	
Uricacidemic														
Ros. 6 ms.	33.6	29.6	6.7	.....	.....	9.9	363	330	650	.....	.....	.....	.....	
H. N. 5 ms.	33.5	20.0	6.9	1.3	.....	8.7	360	210	382	.....	.....	.....	.....	Cardiac
Orl. 4 ms.	48.0	34.8	4.7	.....	.....	10.0	.....	433	440	3.15	1.28	4.43	2.1	
Hai. 7 ms.	43.5	32.2	3.8	.....	.....	.....	.....	351	753	.....	.....	.....	.....	
Pet. 5 ms.	33.3	41.0	11.4	.....	.....	8.2	322	185	905	3.43	4.57	8.00	0.8	Bilirub. 2.5 mgs %
Eclampsia														
Wal. 9 ms.	29.0	34.6	5.5	.....	.....	8.8	370	.....	553	.....	.....	.....	.....	
Bat. 8 ms.	33.0	37.0	7.7	1.2	.....	9.3	362	210	519	.....	.....	.....	.....	
Rya. 8 ms.	34.0	32.4	8.7	.....	.....	8.8	346	260	343	.....	.....	.....	.....	
Mo. 9 ms.	41.0	44.8	5.8	1.2	.....	9.2	318	368	420	.....	.....	.....	.....	
Ag. post.	26.0	93.3	9.1	3.9	.....	9.3	319	204	705	.....	.....	.....	.....	Post part.
" "	33.0	32.7	3.5	1.5	.....	11.0	355	.....	430	.....	.....	.....	.....	One week later

THE USE OF IODIN IN THE TREATMENT OF DISEASES OF THE THYROID GLAND

HENRY ELSNER MARKS

(Summarized from the paper delivered before the New York Academy of Medicine May 21, 1925)

The empirical use of iodin in the treatment of goiter is of remote origin. In 1895 Baumann announced the discovery of iodin as a normal constituent of the thyroid gland and since that time innumerable attempts have been made to relate the various forms of thyroid disease to disturbances in iodin metabolism and to apply iodin, or iodin-containing desiccated normal glands, to the treatment of these disorders. Frequently, in hyperthyroidism, an exacerbation of symptoms followed such attempts and as a result clinical literature abounds with warnings against the use of iodin in exophthalmic goiter. Kocher taught that iodin must never be given and Mellanby states that in the discussion on the treatment of exophthalmic goiter at the Royal Society of Medicine in 1923 no speaker mentioned the use of iodin or any iodin preparation.

In 1909 Marine published his studies on the anatomy and physiology of the thyroid, showing the relation between iodin content, hyperplasia and colloid formation. He found that when the iodin content of the gland drops below .1% hyperplasia begins, and that when iodin is supplied regressive changes occur, the hyperplastic tissue reverting to colloid-filled vesicular tissue of the normal form. From this he concluded that a colloid goiter is a gland which was once hyperplastic but which has reverted to the resting stage without complete reversion to normal in size. In calling attention to the effect of iodin upon hyperplasia, he warned against the use of large doses, and showed that minute amounts of iodin are sufficient to bring about regression. The isolation by Kendall of the physiologically active iodin-bearing secretion of the thyroid gland in 1916 furnished the basis for further important studies of the quantitative relationship of iodin to thyroid activity. Such studies were made possible by

the use of the basal metabolic rate as a quantitative measure of thyroid activity, as initiated by DuBois. As a result of these studies Plummer has lately again called attention to the use of iodin in thyroid disease. He restricts its use to the pre-operative treatment of exophthalmic goiter and the treatment of post-operative reactions. He distinguishes between exophthalmic goiter with diffuse hyperplasia, in which he believes the thyroid product to be an abnormal thyroxin, and the circumscribed enlargements or adenomatous goiters which, when toxic, he believes elaborate an excessive amount of normal thyroxin. He also states that simple adenoma may become hyperactive when treated with iodin. His reason for using iodin only as preliminary to operation in exophthalmic goiter is that the control of symptoms by iodin cannot usually be maintained for more than a few weeks.

In studying the effect of iodin on patients with thyroid disease at the Vanderbilt Clinic, we determined to treat a series of cases with this agent for as long a period of time as it was possible to keep symptoms under control, and resort to surgery only if iodin and X-ray failed. Some of these patients were treated with iodin alone, others with both iodin and X-ray. In no case was it possible to secure complete relief from physical and mental stress. A few of the patients stopped working during the period when their symptoms were most pronounced, but aside from this they went about their usual activities.

Case 1. A woman admitted in August, 1922, age 64, with diabetes. Complained of weakness and nervousness. The thyroid showed circumscribed enlargement. No eye signs, no tremor. The heart was enlarged, B.P. 169/88, P.R. 132. Only the diabetes was treated at first. In February, March, April, May and September, 1924, and March, 1925, X-ray treatments were given. Lugol's solution was also given during parts of this time. Despite these measures the pulse rate has continued to range between 112 and 160 and the BMR from plus 20% to plus 48%. Subjective condition however is very much improved. Pulse rate still 140 but she looks healthy and well, and says she feels "all right." Operation recommended, but refused.

This is the only case in which we have as yet felt it necessary to recommend surgery, and here only because of the persistent

tachycardia. There are no other signs of thyroid intoxication, there is scarcely any enlargement of the gland, and there is considerable doubt as to whether the tachycardia is due to present hyperthyroidism.

Case 2. Man aged 33, with fairly typical exophthalmic goiter of three years duration. Nervousness, tremor and exophthalmos, with excessive perspiration. Pathological eye signs all present. P.R. 100. BMR plus 35%, with basal pulse rate during the test 108. The thyroid is soft and vascular, with moderate diffuse enlargement. There is little discrepancy between the usual pulse rate and the basal rate. After one week on Lugol's solution, ten drops daily, the P.R. dropped from 98 to 80, he felt stronger, less nervous, and had less palpitation, and the thyroid decreased a little in size. The iodin was now increased to 25 drops daily, and the patient's weight increased ten pounds in a month. With this increase in weight the pulse rate rose again and a ten days interruption of the iodin sent it up still further to 110. A series of four X-ray treatments over a period of ten weeks was now given, combined with resumption of iodin, with the result that the pulse rate dropped to 60, the thyroid became much smaller, the BMR fell to minus 15%, the weight rose again almost fifteen pounds, and the patient resumed work with practically no symptoms. For the past five months there has been no treatment. The weight has dropped again, but the P.R. is now 72, the BMR plus 10%, and the thyroid is just palpable. Exophthalmos is slight. If there are any future recurrences it will be interesting to see whether they can be as easily controlled.

Case 3. Man aged 35 whose illness began eleven weeks before admission with lachrymation, protrusion of the eyeballs and enlargement of the neck. Two weeks before admission shortness of breath and a feeling of obstruction in the throat. He had lost about fourteen pounds in a year. There was a very large soft vascular goiter without nodules, marked exophthalmos, tremor and nervousness. The P.R., however, was only 58 and the BMR was 14% below normal. BPR (Basal Pulserate) was 54. The body was apparently withdrawing thyroxin from the gland and destroying it faster than it could be replaced. No treatment was given. Two weeks later the picture had changed. The BMR was now plus 39% and the BPR 92. The thyroid seems now to have been actively producing a substance which was stimulating the metabolic rate. Lugol's was now started in doses of fifteen drops daily, and in three weeks the goiter had diminished markedly in size, the PR was 62, the BMR minus 1%, and the BPR 54. His symptoms had improved greatly. Lugol's was now discontinued. In one week the PR had risen to 66, after a second week without iodin it had gone up to 114, and he complained of substernal and precordial distress. He was put back upon iodin and has not yet returned to the clinic. In this case of acute hyperthyroidism we again see but little discrepancy between the basal pulse rate and the usual pulse rate.

Case 4. A woman of 77 years who has complained of enlargement of the eyes for the past six months. There is no perceptible thyroid enlargement, no sweating and little or no tremor. There is nervousness and insomnia, PR 96, the heart is enormously enlarged, 6 cm. to the right and 14 cm. to the left, B.P. 240/114. The radials are sclerotic, there is retinal sclerosis and evidence of diffuse hyperplastic sclerosis of the smaller vessels as well as decrescent arteriosclerosis. BMR was plus 35%, BPR 88. Lugol's was given at once, thirty minims daily, and within a few weeks the PR was 80, the weight increased four pounds, the BMR dropped to plus 10%, and the patient felt vastly better. At the eleventh week an intercurrent acute respiratory infection sent the PR up to 100 and the BMR up to plus 20%. Iodin was increased for one week, and the BMR again dropped to plus 5% and the BPR to 70.

This case is of interest, not only because of the advanced age of the patient, but because of the obscurity of the clinical picture, the immediate and complete response to iodin, the recurrence of symptoms when an intercurrent acute infection increased the demands of the body upon the thyroid, and the immediate and complete response again to an increase in iodin supply. Here again the discrepancy between BPR and usual PR was slight.

The next case is that of a patient with circumscribed enlargement of the thyroid and marked symptoms of sympathetic instability. Chief among these symptoms is a marked discrepancy between the usual PR and the pulse rate under basal conditions, with at the same time marked instability of the metabolic rate so that determination of the true basal rate is difficult, if not impossible. We have noted this syndrome in a number of patients with circumscribed or so-called adenomatous enlargement of the thyroid, but because of limitations of space only three will be cited here. The pulse rate under basal conditions is normal or only slightly elevated, but there is marked tachycardia under ordinary conditions. Tremor, nervousness, palpitation, sweating and insomnia are frequent, and there are often menstrual disturbances. Eye signs and exophthalmos are absent, or present only in slight degree. That the thyroid is implicated in this syndrome is suggested by the shrinkage of the gland and improvement in symptoms upon administration of iodin, but the marked instability of the PR as contrasted with cases of typical exophthalmic goiter indicates the presence of an added factor.

Case 5. A woman aged 45 with circumscribed enlargement of the thyroid, non-vascular. She is nervous and weak, and there are tremor, tachycardia, palpitation, insomnia, and glycosuria. No exophthalmos or eye-signs. B.P. 150/90. PR 120, BPR 80, BMR minus 8%. During the first five months of observation there were three peaks on the weight curve and these corresponded with the appearance of glycosuria and elevation of the pulse rate. Lugol's was then given, 15 drops daily for three weeks, and the PR dropped at once to 94 despite another increase in body weight. Interruption of iodin for six weeks resulted in a rise in PR to 110. Iodin was then resumed for three months, with disappearance of palpitation, insomnia and nervousness and reduction of the thyroid enlargement. During the 7 months since iodin was discontinued a moderate tachycardia has persisted, the PR varying from 94 to 106, but the thyroid enlargement has disappeared and the patient continues to feel well in all respects. The BPR remains at 80. The metabolic rate is still unstable and successive graphs, taken at intervals of only a few minutes, show marked variations.

Case 6. A woman aged 46 with circumscribed thyroid enlargement dating from her first pregnancy 12 years ago. Severe nervousness and palpitation began 1 year ago. PR 106, BPR 90, BMR plus 25%. Lugol's solution in doses of 10 drops daily for 2 weeks brought the PR down to 88, with improvement in the symptoms. Upon discontinuing iodin for 1 month the PR rose to 120, while 2 weeks after resuming it in doses of but 5 drops daily the PR dropped again to 70 and all nervousness disappeared. Iodin was continued in small doses and 7 months later the BMR was plus 1%, BPR 80 and PR likewise 80. The patient felt very well and there was no nervousness. She then had an attack of grippe and was in bed for 2 weeks with fever, during which time she stopped taking iodin. When she reappeared her PR was 115, BMR plus 29%, though the BPR remained at 80. Large doses of iodin in a week brought the BMR down to plus 6%, with PR and BPR both at 80. She feels and looks well and the thyroid is scarcely palpable.

This case again illustrates the effect of iodin upon this syndrome, with relief of symptoms, shrinkage of the thyroid enlargement, and stabilization of the pulse rate. It also shows again the effect of an intercurrent acute infection in increasing the demands of the body upon the thyroid.

Case 7. This woman first came to the clinic 12 years ago, at the age of 37, with severe diabetes. She had a moderate irregular enlargement of the thyroid, with nervousness, palpitation, tachycardia and tremor, the PR ranging between 100 and 130. During this entire period the symptoms remained about the same, no progression or improvement being noted. Over 2 years ago Syr. Ferrous Iodid was given for 1 month, with a drop

in PR from 130 to 100 and immediate rise again when the iodin was discontinued. Ten months later the BMR was plus 50%. Two X-ray treatments were now given and were followed by a drop in the BMR to minus 2%, with PR 100 and BPR 76. Two months later there was an increase in PR and Lugol's solution was then given for one month, the PR dropping from 132 to 92. The patient felt much better and the thyroid was much smaller, so iodin was stopped, although the PR continued to be unstable. Eight months later the BMR had risen to plus 10% and the BPR was 92. Lugol's solution was now given for one month in doses of 30 drops daily, following which the BMR dropped to minus 8%, the BPR to 80 and PR to 92. No thyroid enlargement could be made out and the patient felt well.

These patients are still under treatment. They cannot be said to be cured, for two reasons. In the first place, the thyroid may still remain incapable of responding when increased demands are made upon it, without a recurrence of symptoms. In the second place, there may be an underlying fault, outside the thyroid gland, which creates an excessive demand upon the thyroid. We feel, however, that our experience has shown that iodin is, at least in some cases, able to relieve the symptoms when they occur and avert the necessity for surgical treatment. Some cases have not responded so well to iodin, and until a much larger amount of material is available the continued treatment of these cases with iodin must be regarded as experimental. We wish, however, to emphasize that we have encountered no contraindications as yet to the continued use of iodin except failure to respond satisfactorily to it. We have not yet seen an increase in toxic symptoms follow upon the use of iodin, nor have we seen, in patients who responded to iodin at the outset, a later failure to respond.

ON THE MECHANISM OF INSULIN ACTION

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(Delivered before the New York Academy of Medicine May 21, 1925)

The vast amount of research work bearing upon carbohydrate metabolism and Diabetes Mellitus in particular which followed the epoch-making discovery of von Mehring and Minkowski in

1889 (total diabetes as a sequence to total pancreatectomy in dogs), has still failed to penetrate the veil of mystery surrounding the actual etiology of Diabetes Mellitus. If the mechanism of insulin action were known, the knowledge gained thereby might well prove a powerful illuminant in this dark field of pathology. In other words, if we knew how insulin acted in re-establishing the diabetic body's potential toward a normal carbo-hydrate metabolism, we might be able to discover the missing pathological link between the picture as represented by a totally depancreatized dog and a severely diabetic human being. It has been proven that insulin aids in the fragmentation of the sugar molecule in the presence of extracts of certain body tissues such as liver or muscle. It has also been shown that the administration of insulin by injection causes the formation of glycogen in the liver of a depancreatized dog. Insulin may therefore be properly defined as a true hormone, *i.e.*, a pharmacodynamic substance secreted by specialized tissue and carried by the circulation to the sites of its activity. However, the mechanism of the physiological action of this hormone remains obscure. The experimental work to be described was done with the object of gaining an insight into the actual mechanism of insulin action.

I

Diabetics as well as individuals with a normal carbohydrate metabolism were studied. The experiments were done in the morning, with the subject in a fasting condition, or following a breakfast of definite composition finished at a known time. Two experiments on the same individual, employing like doses of insulin (Lilly U–40) from the same ampule, and under the same dietary conditions but differing in the method of administration of the insulin constitute a series, and are so referred to in the text. A total of 33 such series are here reported. The blood sugar was determined before the insulin injection, and at one hour, two hours, and four hours following the injection. In a number of cases the same blood sugar curve, but omitting the insulin injection, was determined. In six additional series of one hour only the blood sugars were determined at twenty minute intervals following the injections.

Twenty-nine (88 per cent.) of the thirty-three series show a greater reduction in the blood sugar level at the first hour following the intradermal injection than following a subcutaneous injection of an equal dose.

At the second hour twenty-three (70 per cent.) of the intradermal injections resulted in a lower blood sugar level than did the subcutaneous injections.

At the fourth hour, twenty, or 67 per cent., of the series showed a greater hypoglucemia with intradermal administration.

The difference in the response to the two methods of administration as manifested by the hypoglucemic effect is most striking with the smallest doses (*i.e.*, 5 units) and at the first hour after the injection. The maximum difference falls at the first hour and there is a gradual decrease in this difference at the subsequent time intervals.

This difference in response to the two methods of administration varies from case to case. The greatest differences in the hypoglucemic effect occur in the cases of moderately severe diabetes. The least differences were noted in non-diabetics. A consistently less great response to the intradermal injection occurred in one case of severe diabetes.

Insulin injected subcutaneously enters the blood stream and is brought to the tissues more promptly than when the same dose is given between the layers of the skin. Kasahara[1] showed that the resorption of true solutions, colloidal solutions and cell and bacterial suspensions when introduced intracutaneously is materially delayed as compared to identical injections administered subcutaneously. Our results cannot therefore be explained by a quicker resorption of the intradermally introduced insulin. From the results of the 20 minute series it was apparent that there is a blood sugar lowering effect of intradermally injected insulin before any of the hormone can possibly be present in the blood stream, for the subdermally administered equal dose of insulin shows no such effect twenty minutes after the administration. We conclude from the observations reported above that insulin injected intracutaneously must have an initial specific

[1] Kasahara, Zeitschr. f. d. ges. exp. Med. 1925, XLIV, 294.

action produced in some way other than through the usual contact of the hormone with the tissue fluids and cells.

II

Our findings imply the transmission of a specific stimulus between the intracutaneous area of the skin and the organ or organs the activity of which governs the carbohydrate metabolism in the mammalian body. We postulate the pathway which carries this stimulus to be the fibers of the parasympathetic nervous system. Claude Bernard showed that stimulation of certain parts of the parasympathetic system results in increased glucose formation in the body. M. Eiger,[2] working with turtles, showed that stimulation of the peripheral end of the cut vagus caused increased glycogenesis, despite exclusion of the pancreatic activity. H. Meyer[3] showed that injection of pancreatic extract inhibits glycogenolysis in the liver. From these experiments it is to be assumed that stimuli may travel via the vagus nerve to the liver and there cause actual increased liver cell metabolism, and also that such stimuli may travel to the pancreas, whereby an equivalent internal secretory influence of the liver cell metabolism may be registered. In both cases vagus stimulation results in the inhibition of glycogenolysis. Minkowski's experiments[3] have shown that not only extirpation of the pancreas but also disconnection of the nerves between pancreas, liver and duodenum results in diabetic symptoms.

The response of the liver cell in the form of glycogenetic activity is governed to a large extent by the amount of glycogen in the liver at the time, and this response will be decreased if the liver is rich in glycogen. In two non-diabetics the blood sugar levels following the injections of 10 and 20 unit doses of insulin intradermally as well as subcutaneously were studied. It was found that there was a quick recovery to the normal blood sugar level in both, as well as a reversed response in one of the subjects. These results can be accounted for on the basis of the degree of glycogen saturation of the liver cells.

[2] Eiger, Centralbl. f. Physiol. XXX.

[3] Quoted from L. R. Mueller, Die Lebensnerven, Berlin, Springer, 1924, 282.

III

The glucolysis occurring in the bloods drawn before insulin injection and at stated intervals thereafter was determined in nine series. The average of the absolute values in mgs per cent. of the sugar destroyed when the blood was allowed to remain in the incubator at 37 ° C. for two hours were as follows:

	Insulin by intradermal method	Insulin by subcutaneous method
Before injection	24 mgs. %	21 mgs. %
One hr. after injection	19 mgs. %	28 mgs. %
Two hrs. " "	22 mgs. %	30 mgs. %
Four hrs. " "	15 mgs. %	21 mgs. %

As may be seen from the table the one-hour post intradermal-injection blood failed to manifest greater glucolytic activity than did the blood drawn before insulin injection. On the other hand, the one-hour post subcutaneous-injection blood manifested a greater glucolytic activity than did the blood drawn before the injection. In fact the glucolytic activity of the blood drawn following intradermal injection remained constant or diminished slightly as the blood sugar level decreased, whereas by the subcutaneous method the glucolytic activity of the parallel blood was increased at the two-hour post injection period as well as at the one-hour post injection period.

In severe diabetes the glycogenetic function of the liver is markedly reduced or is even absent. The severity of the diabetic condition is mirrored by the results of the various series as done in these experiments in that the concentration of glycogen in the liver cells governs the degree of difference in response to the two methods of injection.

IV

Experiments done by one of us[4] on rabbits proved that if the parasympathetic pathways are blocked by atropin the normal blood sugar lowering effect of intradermally injected insulin does not appear. In control tests it was shown that atropin itself in the doses used does not affect the blood sugar level. If rabbits

[4] E. F. Mueller. To be published.

are injected with atropin every 30 minutes and the parasympathetic pathways are thus cut off during the entire period of observation, the result upon the animal's reaction to various methods of insulin administration is as follows: The blood sugar curve following intravenous administration is the same as the curve in the same animal without atropin. After subdermal injection the hypoglucaemic effect is slightly less marked than in the non-atropinized animal. If the insulin is administered intracutaneously in an atropinized rabbit the blood sugar level is not affected for a period of almost an hour. During the two succeeding hours a hypoglucaemic effect is noted, but it is only half as great as in a non-atropinized animal.

These experiments indicate that the fibers of the parasympathetic nervous system may carry the specific stimulus initiated by the insulin injection, if given intradermally or subdermally. That area in the body which is most rich in the parasympathetic nerve endings will serve as the most effective area for the localization of the depot if the reaction to this effect is to be given the greatest prominence. This effect is totally lacking in the intravenous administration, partly demonstrable by the subdermal administration, and very much more definitely present when the insulin is deposited intracutaneously. The degree of intensity of this stimulus does not depend upon the dosage; the effect of this stimulus, though gradually diminishing, will persist as long as the deposit of active insulin remains. With the beginning of resorption of the insulin from the depot wherever located, into the circulation, the hormone effect is initiated, and increases with increasing concentration of the active insulin in the circulation. As resorption into the circulation proceeds, the hormone effect increases and reaches its maximum, and the specific effect of the stimulus via the parasympathetic nervous system gradually diminishes and disappears.

Irrespective of the condition of the subject's carbohydrate metabolism at the time of the experiments, it was found that under conditions as nearly constant as possible, the two methods of administration differed in their effect upon the blood sugar level. As between one case and another this difference could not

be interpreted as a criterion of the clinical severity of the disease. But it is possible that a study of the difference in the blood sugar level in the individual diabetic patient resulting from intradermal and subcutaneous injections of insulin may prove a useful basis for a revised clinical classification of the disease. Such studies might also conceivably have a bearing upon prognosis and treatment.

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